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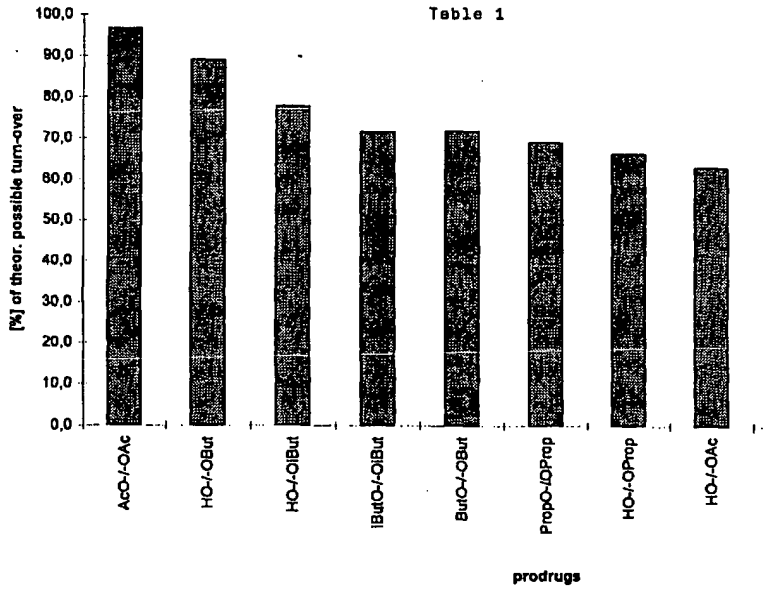
(54) Novel derivatives of 3,3-diphenylpropylamines

(57) The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly the invention concerns to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h

Table 1



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Description

[0001] The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

[0002] More particularly, the present invention relates to certain prodrugs of 3,3-diphenylpropylamines while avoiding on administration to a mammal a high variation in bioavailability and formation of active metabolites which can result in a substantial variation in response - too low efficacy or too much side effects - for the subjects on the suggested therapy.

[0003] In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions but also the main part of the contractions in the overactive bladder resulting in symptoms as urinary frequency, urgency and urge incontinence. For this reason antimuscarinic drugs have been instituted as a treatment of bladder over activity.

[0004] Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder over activity. The effectiveness of oxybutynin has been demonstrated in several clinical studies but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the must common experienced side effect which may be severe enough to result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

[0005] Tolterodine is a new, potent and competetive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al, 1997, Tolderodine - a new bladderselective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies.. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

[0006] A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite is almost identical to those of tolterodine (Nilvebrant et al, 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite give a major contribution to the clinical effect in most patients.

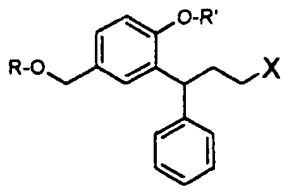
[0007] The document WO 94/11337 discloses that the active metabolite of tolterodine is suggested as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage compared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

[0008] However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability. In a method to circumvent this disadvantage different prodrugs of the metabolite have been synthetized and tested for their absorption/bioavailability data.

[0009] It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is an further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption/bioavailability after oral administration of the drugs or an unfavourable metabolism.

[0010] The novel compounds of the present invention are represented by the general Formula (I)

(I)



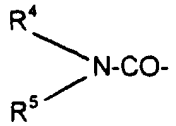
wherein R indepently signifies:

a) R^1 represents the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl or allyl; or

b) R^2 represents the residues formyl, acetyl, propionyl, isobutyryl, butyryl, valeroyl, pivaloyl, benzoyl; or

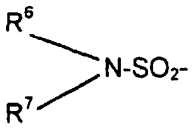
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

d) a group consisting



of wherein R^4 and R^5 indepently represent the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

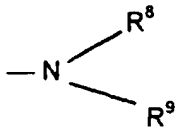
e) a group consisting



of wherein R^6 and R^7 indepently represent the residues methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl; or

f) an ester of inorganic acids such as sulfuric acid, phosphoric acid;

X represents a tertiary amino group of Formula Ia



(Ia)

wherein R^8 and R^9 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen, R' represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, alkyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, if R is hydrogen R' will not represent hydrogen or methyl
and

their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

[0011] The compounds of Formula (I) can form salts with physiologically acceptable acids, organic and inorganic. Furthermore the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid

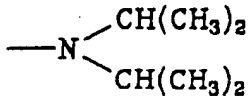
addition salts include the hydrochloride, hydrobromide and the like.

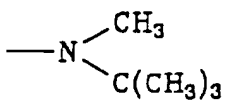
[0012] When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

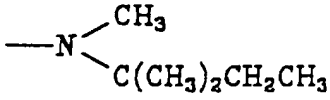
[0013] Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

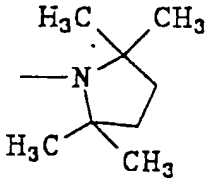
[0014] According to an other embodiment of the invention at least one of R^8 and R^9 comprises a branched carbon chain.

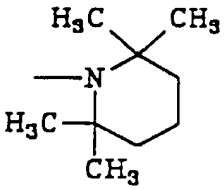
[0015] Presently preferred tertiary amino groups X in Formula I include the following groups a) to h):

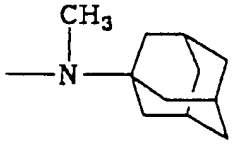
a) 

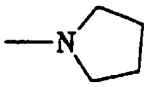
b) 

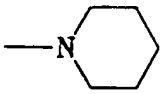
c) 

d) 

e) 

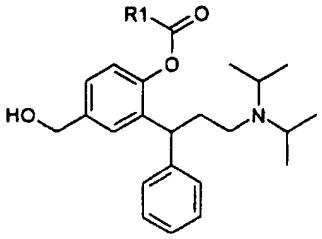
f) 

g) 

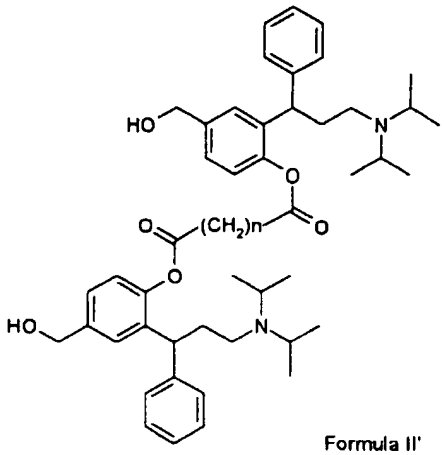
h) 

[0016] Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general Formulae II and II'



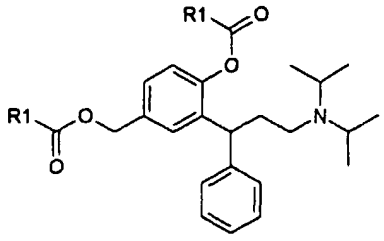
Formula II



Formula II'

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester
Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester
Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester

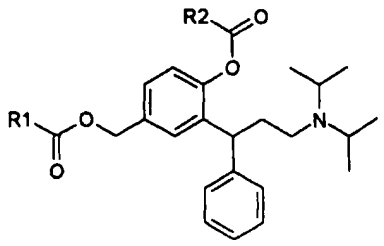
B) Identical diesters represented by the general Formula III



Formula III

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester
n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester
Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

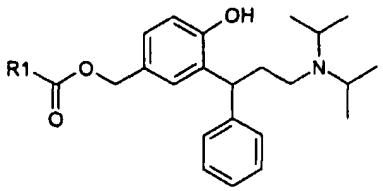
C) Mixed diesters represented by the general Formula IV



Formula IV

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)benzyl ester
2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

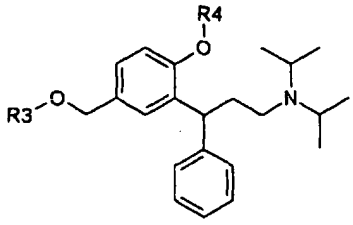
D) Benzylic monoesters represented by the general Formula V



Formula V

Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester

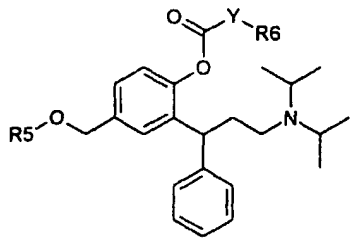
E) Ethers and silyl ethers represented by the general Formula VI



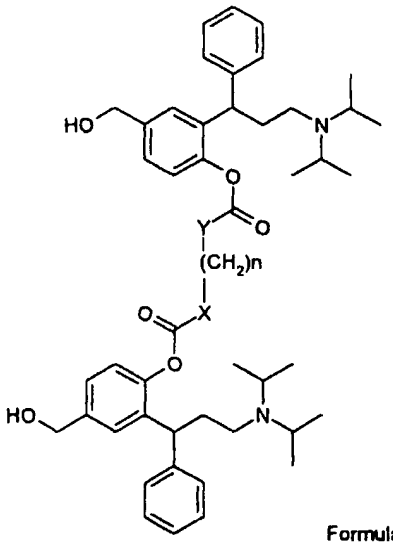
Formula VI

2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol
Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)propyl]-amine
[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol
Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
(4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)phenyl]-3-phenylpropyl}-diisopropylamine
[4-(tert.-Butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol
Acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
4-(tert.-Butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)phenol
{3-[2-(tert.-Butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)phenyl]-2-phenylpropyl}-diisopropylamine
Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester

F) Carbonates and carbamates represented by the general Formulae VII and VII'



Formula VII



Formula VII'

N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester

N-Phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester

[0017] The compounds of formula (I) may, in accordance with the present invention be prepared by per se conventional methods. Methods for preparing substituted 3,3-diphenylpropylamines as disclosed by this invention may be synthesized according to methods as described in the document PCT/SE93/00927.

[0018] The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

[0019] The following starting materials and preffered Examples illustrate the invention:

I. Experimental

1. General

[0020] All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy. The chemical shifts reported (^{13}C NMR, ppm) refer to the solvents $CDCl_3$ (77.10 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm) respectively. Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution. Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%). Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-Cl) or negative (N-Cl) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.

2. Synthesis of Intermediates A and B

[0021] An icecooled solution of 4-bromophenol (69.2g) and cinnamoyl chloride (66.8g) in dichloromethane (150ml) was treated with triethylamine (40.6g). After stirring for 18h at room temperature the mixture was washed with water (250ml), 1M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0g, 99.8% yield), m.p. 113.3 °C, tlc (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

[0022] A portion of the ester (60.0g) was dissolved in a mixture of acetic acid (60ml) und concentrated sulphuric acid (18ml) and refluxed for 2h. After cooling, the reaction mixture was poured into ice water and the product was was isolated by extraction with ethyl acetate. Evaporation of the solvent and recrystallization of the residue from boiling I ethanol (150ml) yielded 26.3g (43.8% yield) of pure, crystalline *6-bromo-4-phenylchroman-2-one,* m.p. 117.8 °C, tlc (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89. 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

[0023] A suspension consisting of 6-bromo-4-phenylchroman-2-one (85.0g), anhydrous potassium carbonate (46.7g), sodium iodide (20.5g) and benzyl chloride (40.6g) in methanol (350ml) and acetone (350ml) was refluxed for 3h. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300ml) and the extract was washed with water (2 x 200ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8g (102.1 % crude yield) of *3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc (1) 0.77. NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77,126.46, 126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

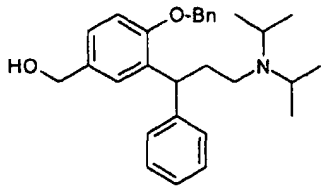
[0024] A solution of the propionate (121.0g) in 350ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9g) in tetrahydrofuran (350ml). After stirring at room temperature for 18h, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8 °C, tlc (1) 0.47, *3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol*. NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

[0025] A cooled (5 °C) solution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0g) in dichloromethane (300ml) war treated with pyridine (79.4ml) and than p-toluenesulphonyl chloride (60.6g) in dichloromethane (200ml). After 18h at room temperature the solvent was removed in vacuum and the residue extracted diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3g, 93.6% yield), tlc (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

[0026] A solution of the toluenesulphonate (139.3g) in acetonitrile (230ml) and N,N-diisopropylamine (256g) was refluxed for 97h. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500ml) and aqueous sodium hydroxide (2M, 240ml). The organic phase was washed twice with water (250ml) and then extracted with 1M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5g, 77.9% yield), tlc (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70. 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

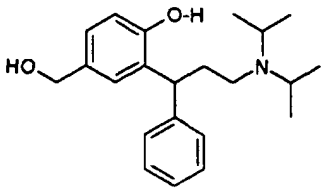
[0027] An ethereal Grignard solution, prepared from the above amine (22.8g), ethyl bromide (17.4g) and magnesium (6.1g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200ml) and then cooled to -60 °C. Powdered solid carbon dioxide (ca. 50g) was the added in small portions and the green reaction mixture was warmed at room temperature. After the addition of an aqueous solution of ammonium chloride (200ml, 10%) and adjustment of the aqueous phase to pH 0.95, a white solid was recovered by filtration to provide *4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)benzoic acid hydrochloride* (14.7g, 64.3% yield), m.p. 140 °C (dec.), tlc (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

[0028] The hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free base thus obtained (28g) was dissolved in dry diethyl ether (230ml). This solution was slowly (2h) dropped under an nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8g) in ether (140ml). After stirring for 18h, the reaction was quenched by the addition of water (4.7ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (26g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4 °C, tlc (2) 0.32, **Intermediate A**. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



(Intermediate A)

[0029] A solution of Intermediate A (9.1g) in methanol (100ml) was hydrogenated over Raney-nickel (4.5g) under ambient conditions. After 5h thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95g, 96.5% yield) which gradually solidified, *2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50 °C, tlc (2) 0.15, **Intermediate B**. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38. Hydrochloride: colourless crystalls, m.p. 187-190 °C (with decomposition)



(Intermediate B)

3. Examples

a) Phenolic monoesters

aa) General Procedure

[0030] A stirred solution of *2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (Intermediate B, 1.71g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid monochloride for compounds of Formila II, 2.50 mmol for compounds of Formula II') in 60 ml of dichloromethane was cooled to 0 °C and then triethylamine (0.502g,4.96 mmol for compounds of Formula II, 1.05g, 9.92 mmol for compounds of Formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 mm. Stirring was continued for 18h at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and a low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents. The esters of Formula II or II' were obtained as viscous colourless to light yellow syrups in purities between 90% and 99% (tlc, HPLC, NMR).

bb) Salt formation (Example hydrochloride)

[0031] A cooled (0 °C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of Formula II) or 9.4 mmol (diamines of Formula II') ethereal (1M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100 °C (with decomposition).

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16, 43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-CI (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-CI (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); ; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.43(4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36;

2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92,

128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; ; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, R_f 0.52 (4); NMR ($CDCl_3$): 20.42, 20.62, 36.95, 41.72, 42.27, 48.23, 64.83, 122.74, 125.33, 127.36, 127.89, 127.97, 128.38, 129.34, 130.64, 131.15, 131.83, 136.87, 138.90, 143.82, 147.74, 164.77

Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.38 (4); NMR (CDCl3): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23, 64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.40 (4)
NMR (CDCl3): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.43; NMR (CDCl3): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 122.85, 127.39, 127.99, 128.35, 129.31, 131 .84, 136.98, 138.94, 143.80, 147.40, 147.40, 169.05

Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, R_f 0.43; NMR (CDCl3): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

[0032] Identical diesters (Formula III) were prepared and worked-up as described above with the exeption that 2.4 mmol of both triethylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.65 (4) This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F: Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta* **37**: 45 - 58 [1954])

Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.76 (4);; GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GO-MS/P-CI (methane, trimethylsilyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$): 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80,65.21,123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; ; GO-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76, 148.41, 171.68, 173.40; ; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, R_f 0.83 (4); NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane,): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.69 (4); NMR (CDCl3): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

c) Mixed diesters

[0033] Mixed diesters (Formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Workup and physical properties corresponded to the bases and salts described above.

Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.71, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18;

2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-*phenylpropyl)-benzyl ester*, R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)phenyl ester, R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

[0034] A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 h complete disappearence of the starting material (R_f = 0.45 (3). The mixture was filtered and then evaporated under high vacuum (< 40 °C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.26 (2); NMR ($CDCl_3$): 19.45,20.96, 33.26, 39.63, 42.27, 48.23, 48.23, 63.59, 118.00, 127.36, 128.33, 128.33, 128.48, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, R_f 0.77 (4); NMR ($CDCl_3$):18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

[0035] A mixture of Intermediate B (3.4g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^3-OH, (50 - 150 ml) was stirred at room temperature until no starting material was detectable (2 - 24 h). After evaporation to dryness (< 35 °C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100 - 200 ml, 5 %, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of Formula VI (R^4 = H) as colourless to light yellow oils.

[0036] Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for Examples of the structure of Formula IV.

Hydrochlorides:

[0037] Molar equivalents of bases of Formula VI (R^4 = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile to give colourless crystalline material.

2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%); hydrochloride: amorphous hygroscopic colourless solid; m. p. 161 °C; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85

2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol, R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 444.8 (100%), 398.4 (6%); hydrochloride: m. p 158 - 161 °C, NMR (CD_3OD): 15.43, 17.12, 18.82, 33.80. 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethyl-phenol, NMR ($CDCl_3$): 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65

2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28, 39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethyl-phenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128.35, 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.10, 0.29, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14 155.06

Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.48, 128.44, 133.37, 135.74, 144.11, 155.20

4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol, R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85), 470.43 (10%), 396.3 (31%)

Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)phenyl ester, NMR ($CDCl_3$): -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine, R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7 (78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.87 (4); NMR ($CDCl_3$):20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05,137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01); GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and Carbonates

[0038] A solution of 4.0 mmol of Intermediate B or benzylic ether (Formula VI, R^4 = H) in dichloromethane (20 ml) was treated at room temperature for 16 h with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation the oily residue was redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides. Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65 °C over 18 h.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of Formula II to IV. Alkyl chloroformates were used as acylation reagents.

N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m. p. 64 °C (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester, R_f 0.36 (3), NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

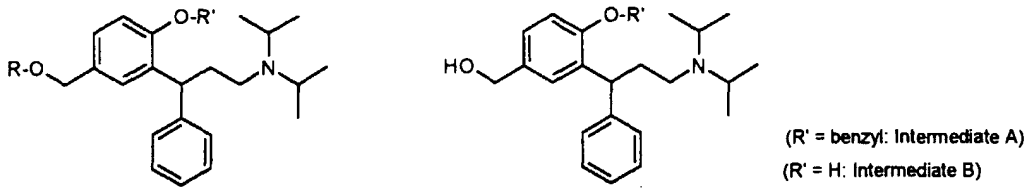
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester, (Formula VII', X = Y = NH, n = 4) R_f 0.60 (6); dihydrochloride: m. p. 142.5 - 145.6 °C

Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

4. The respective prodrugs (Formula I) or pharmaceutically acceptable salts thereof were prepared also from Intermediate A or Intermediate B by the following methods:

[0039]

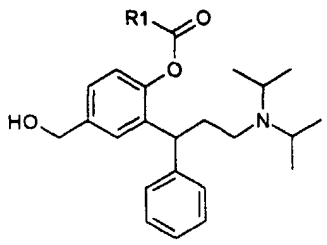


(R' = benzyl: Intermediate A)
(R' = H: Intermediate B)

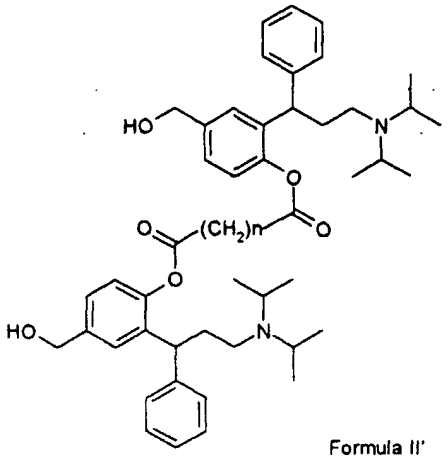
Formula I

a) Phenolic monoesters

[0040] Treatment of Intermediate B with an equivalent of an acylating agent (e.g. acyl halogenide or acyl anhydride) in an inert solvent and in the presence of an condensating agent (e.g. amine) provides phenolic monoesters of Formula II or Formula II' (n = 0-12), respectively, if polyfunctional acylating agents (e.g. acid chlorides of dicarboxylic acids) are used.



Formula II

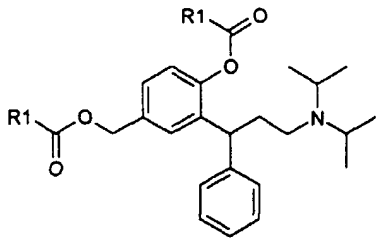


Formula II'

[0041] Alternatively, structures of Formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, „*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991).

b) Identical diesters

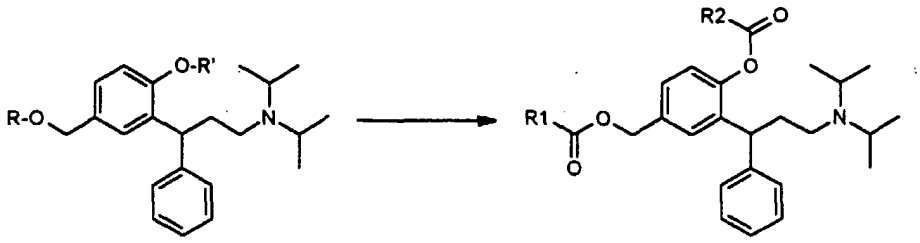
[0042] Di-acyl compounds are readily accessible if an at least two molar excess of acylation agent is used in the above-mentioned conversions of Intermediates A or B or, more general, on treatment of compounds of Formula I with acylating agents in the presence of suitable catalysts.



Formula III

c) Mixed diesters

[0043] Acylation of compounds of the general Formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions yields mixed diesters of Formula IV, where R^1 and R^2 are different.

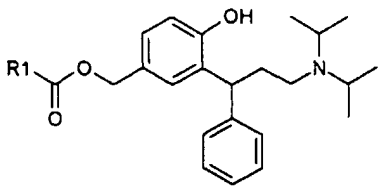


Formula I

Formula IV

d) Benzylic monoesters

[0044] Moreover, the invention refers to the preparation of phenols with *para* acyloxymethyl substituents (Formula V). These compounds can be prepared in several chemical steps from intermediates such as Formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P. G. M. Wuts, „*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, in the present invention that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room temperature and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

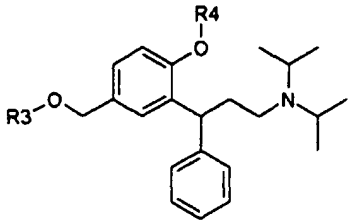


Formula V

e) Ethers and silanyl esters

[0045] Regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J. M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P. M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or Formulas II or VI (in which R^3 hydrogen) or Formula VII (in which R^5 is hydrogen) as well as benzylic acylates such as Formula III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^4 = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).



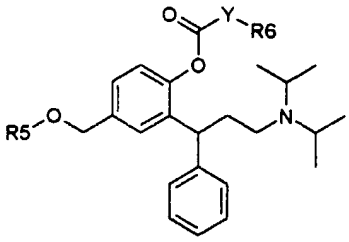
Formula VI

f) Carbamates and Carbonates

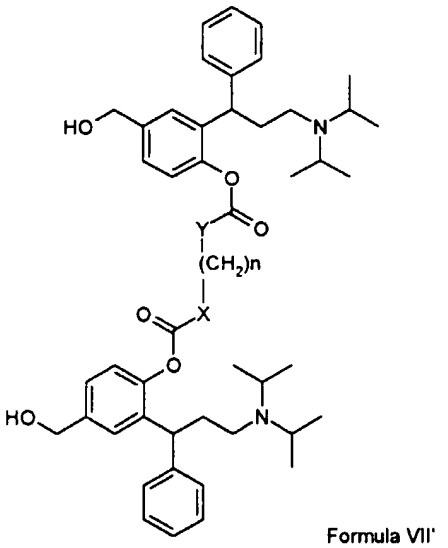
[0046] Other reactive reagents which can be used in the reaction of the hydroxy groups of Intermediates A or B, Formulas II, II', V, or VI (R^3 or R^4 = hydrogen) shown above are, for example, other activated carbonyl compounds or carbonyl precursor reagents.

Preferably, haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates, isothiocyanates can be used. The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10 °C to the refluxing temperature of the solvent or reagent used to provide compounds of the general Formula VII where R^5 represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and Y and R^6 represent O, S, NH and alkyl or aryl, respectively.

Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of Formula VII' where X, Y have the meaning of O, S, or NH and n is zero to twelve.



Formula VII



Formula VII'

[0047] The compounds of formula (I) can be used as pharmaceutically active substances, especially as antimuscannic agents.

[0048] The compounds of formula (I) can be used for preparing pharmaceutical formulations containing at least one of said compounds.

II. Pharmaceutical composition of the present invention

[0049] In accordance with the present invention, the compounds of formula (I), in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of formula (I) in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

[0050] The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

[0051] The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

[0052] The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0,05 mg to about 200 g each.

III. Incubations of different compounds of the invention with human liever S 9-fraction.

[0053] A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

[0054] The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

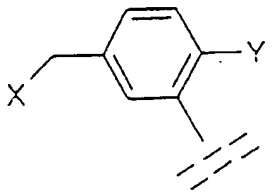
[0055] The analysis was performed by a routine High Pressure Liquid Cromatography (HPLC) method with UV-detection.

[0056] The incubation results expressed in (%) of theoretical turn-over are presented in Table 1.

[0057] They ranged from 96 to 63,2 %. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:

[0058] The prodrugs introduced in the assay show the following chemical structure:

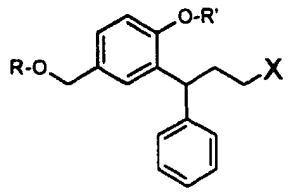


chemical structure X-/-Y

AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate
iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	butyrate
PropO-/-OProp	means	propyrate
HO-/-OProp	means	hydroxy and propyrate
HO-/-OAc	means	hydroxy and acetate

Claims

1. 3,3-Diphenylpropylamines of Formula I:



(I)

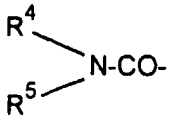
wherein R indepently signifies:

a) R^1 represents the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl or allyl; or

b) R^2 represents the residues formyl, acetyl, propionyl, isobutyryl, butyryl, valeroyl, pivaloyl, benzoyl; or

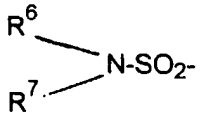
c) R^3 represents the residues CH_3OCO-, C_2H_5-OCO-, C_3H_7OCO-, $(CH_3)_3COCO$-, benzoylacyl, benzoylglycyl, glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl; or

d) a group consisting of



wherein R^4 and R^5 indepently represent the residues hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl and wherein R^4 and R^5 may form a ring together with the amine nitrogen;
or

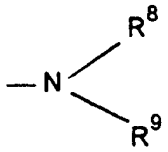
e) a group consisting of



wherein R^6 and R^7 indepently represent the residues methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl; or

f) an ester of inorganic acids such as sulfuric acid, phosphoric acid;

X represents a tertiary amino group of Formula Ia



(Ia)

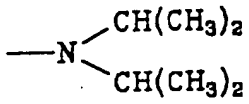
wherein R^8 and R^9 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms and wherein R^8 and R^9 may form a ring together with the amine nitrogen, R' represents hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, alkyl, phenoxyalkyl wherein the alkyl residue means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, if R is hydrogen R' will not represent hydrogen or methyl
and

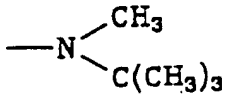
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

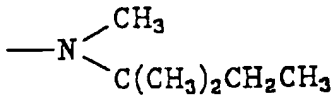
2. 3,3-Diphenylpropylamines according to claim 1, wherein each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

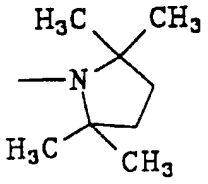
3. 3,3-Diphenylpropylamines according to claim 1 or 2, wherein at least one of R^8 and R^9 comprises a branched carbon chain.

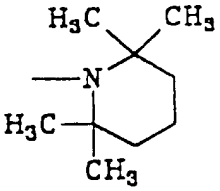
4. 3,3-Diphenylpropylamines according to any one of claims 1 to 3, wherein X signifies any of the following groups a) to h):

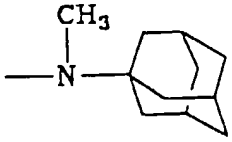
a) 

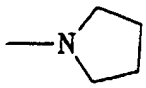
b) 

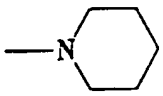
c) 

d) 

e) 

f) 

g) 

h) 

5. 3,3-diphenylpropylamines, their salts with physiologically acceptable acids, their free bases or salts thereof, racemates and individual enantiomers thereof which are definied as

Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethy-phenyl] ester
Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester
Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester

Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester
n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester
Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester
Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol
2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester
Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester
2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol
Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)propyl]-amine
[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol
Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine
[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol
Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)phenyl]-3-phenylpropyl}-diisopropylamine
[4-(tert.-Butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol
Acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
4-(tert.-Butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol
{3-[2-(tert.-Butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)phenyl]-2-phenylpropyl}-diisopropylamine
Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester
N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester
N-Phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester
{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester
Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester

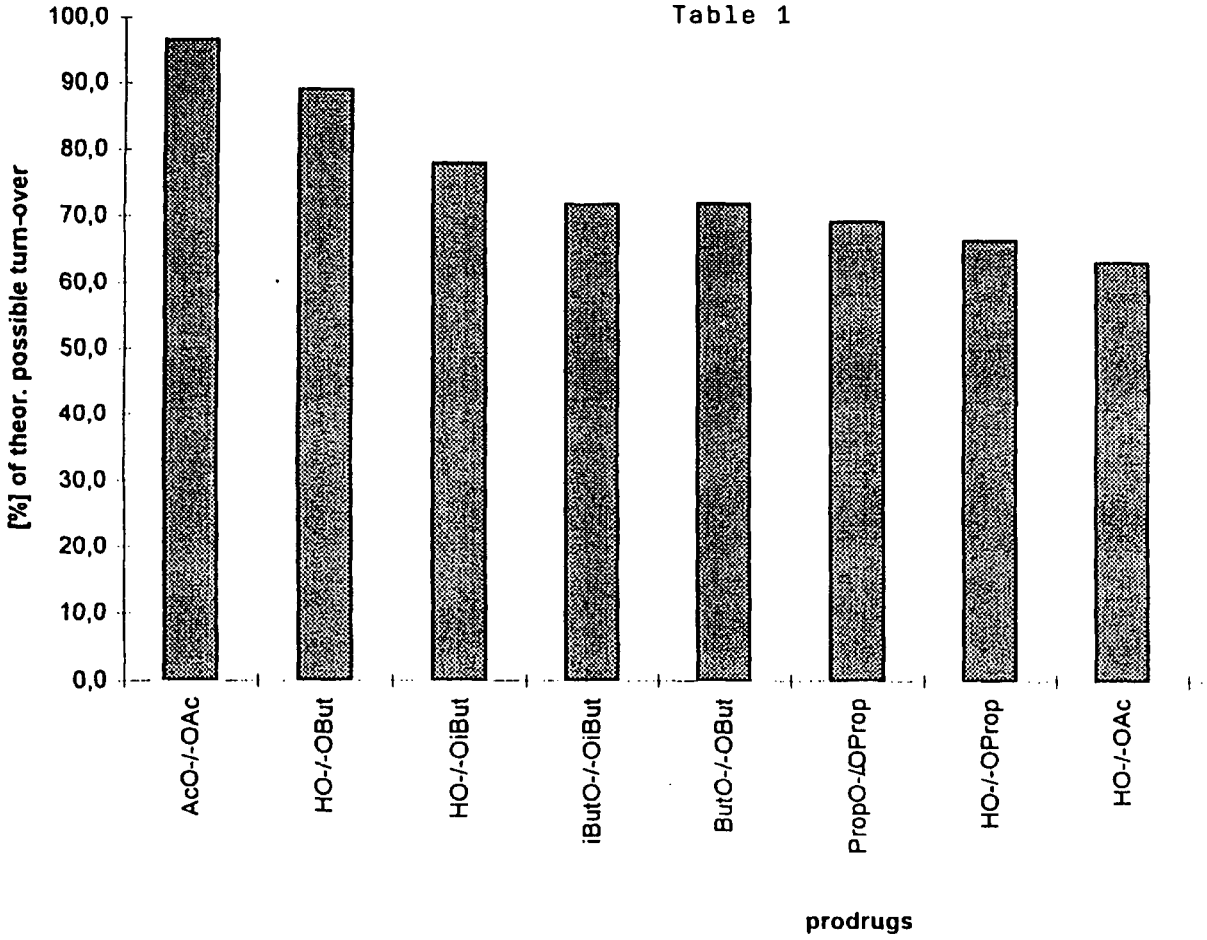
6. 3,3-Diphenylpropylamines according to any one of claims 1 to 5 for use as pharmaceutically active substances, especially as antimuscarinic agents.

7. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1 to 6 and preferably a compatible pharmaceutical carrier.

8. Use of a 3,3-diphenylpropylamine according to any one of claims 1 to 7 for preparing an antimuscarinic drug.

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h

Table 1



European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 10 8608

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,D	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 * page 12, line 35 - page 13, line 15 * ---	1-4,6-8	C07C1/00 C07C217/62 C07C217/48 C07C219/28 C07C219/22
A	WO 89 06644 A (KABIVITRUM AB) 27 July 1989 * abstract * ---	1-8	C07D207/06 C07D295/06 C07C271/08
A,D	LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 * the whole document * -----	1,7,8	C07F7/18 C07C307/02 A61K31/135 A61K31/325 A61K31/40 A61K31/435

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07C
C07D
C07F
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	5 October 1998	Rufet, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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EPO FORM 1503 03.82 (P04C01)

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82